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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/562,627	12/22/2005	Mu-Hyeon Choe	428.1060	6450

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EXAMINER	
KOSSON, ROSANNE	
ART UNIT	PAPER NUMBER
1652	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/562,627	CHOE ET AL.	
	Examiner	Art Unit	
	Rosanne Kosson	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 November 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21,30,31 and 35-55* is/are pending in the application.

4a) Of the above claim(s) *37,38 and 41-47* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21,30,31,35,36,39,40 and 48-55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed on November 28, 2008 has been received and entered. Claims 21, 30, 31, 35, 37, 39-43, 46 and 47 have been amended. Claims 22-29 and 32-34 have been canceled. Claims 48-55 have been added. Claims 37, 38 and 41-47 were withdrawn in the previous Office action as being drawn to non-elected inventions. Claims 21, 30, 31, 35, 36, 39 and 40 were withdrawn in part to the extent that they do not read on the elected invention. Accordingly, claims 21, 30, 31, 35, 36, 39, 40 and 48-55 are examined on the merits herewith to the extent that they read on the elected invention only.

Regarding new claim 52, in accordance with Applicants' species elections of August 23, 2007, the elected sequence in this claim is ISTKASGGGGSGGGGSGGPE.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Sequence Listing and Specification

The disclosure is objected to because of the following informalities. The specification and Sequence Listing are objected to, because the claims have been amended to add claim 52, which recites a polypeptide sequence without an accompanying SEQ ID NO:. A SEQ ID NO: is required, and this sequence must be added to the instant Sequence Listing. The specification must be amended to include a SEQ ID NO: for this sequence. See MPEP §§ 2421-2425. Appropriate correction is required.

Applicants are advised that the sequence recited in claim 52 could not be searched, because a corrected Sequence Listing and sequence identifier (SEQ ID NO:) have not been provided.

Claim Objections

Claim 21 is objected to for lack of clarity in part (iii). This part recites an extension peptide described by two wherein clauses. The wherein clauses indicate that the extension peptide has at least 45 amino acids, but this feature is not recited in the portion that precedes the wherein clauses. For clarity, part (iii) should recite, before the wherein clauses, that the extension peptide is at least 45 amino acids in length.

Claim 30 is objected to for containing clerical errors. The claim recites that the binding domain is "the N-terminal," rather than the N-terminal domain, or located N-terminally relative to the uncoupled Cys. The claim recites that the functional group domain is "the C-terminal," rather than the C-terminal domain, or located C-terminally relative to the uncoupled Cys. Appropriate correction is required.

Claim 52 is objected to because, as discussed above, it recites a polypeptide sequence without an accompanying SEQ ID NO:. A SEQ ID NO: is required. See MPEP §§ 2421-2425. Appropriate correction is required.

Claim Rejections - 35 USC § 112, first paragraph

Claims 21, 30, 31, 35, 36, 39 and 40 are again rejected, and claims 48-55 are rejected, under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Specifically, the claims recite the genus of a binding domain that is any antibody, any ligand or any receptor that

binds to a cell-surface antigen (amended from simply "binding domain"). This rejection was discussed in the previous Office action.

As previously discussed, the specification discloses that the purpose of the claimed monomers and dimers is site-directed drug delivery and that the binding domains that work in the claimed invention are those that bind to cell-surface antigens, cell-surface ligands or cell-surface receptors, particularly those specific for mammalian tumor cells. The binding domain cannot be any protein (in the instant context of a fusion protein) that binds to any other molecule. Although the claims have been amended to recite that the binding domain is an antibody, a ligand or a receptor that binds to a cell-surface antigen, the antibody can bind to any antigen, not just a cell-surface antigen, and a ligand is a protein (in the instant context of a fusion protein) that binds to anything. Thus, the amendment does not overcome the rejection. Nevertheless, Examiner appreciates Applicants' intention to satisfy the written description requirement.

Applicants note that the binding domain need not be a protein; it can be a drug, biosensor, etc. But, the preamble of claim 21 recites a recombinant fusion protein monomer. An enzyme conjugate, particularly a conjugate to a material such as biosensor, which can be a microchip, is not claimed. As a fusion protein, the binding domain is a polypeptide.

Claims 21, 30, 31, 35, 36, 39, 40 and 48-55 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Specifically, the claims recite the genus of an affinity domain for homo- or hetero-multimerization (with homo-dimerization corresponding to the

elected invention). Only three such domains are disclosed in the specification, on pp. 33, 47 and 65, the polypeptides SKPC, CKPS and AKPC. The disclosed species of the claimed genus are insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus, because the polypeptides in the genus can be of any length and any amino acid sequence. Additionally, if only one C is present, the claimed fusion protein, via the affinity domain, can form a dimer with a C-C disulfide bond, but not a multimer or polymer that contains more than two monomers. A sufficient written description of a genus of molecules or compositions may be achieved by a recitation of structural features common to each member (species) of the genus, **which features constitute a substantial portion of each member of the genus**. The only recited features of the genus in these claims are functional limitations, i.e., the functions of homo- or hetero-multimerization. These functional limitations do not constitute a substantial structural portion of each species in the genus, as the structure is completely undefined and the specification does not define the remaining structural features necessary for members of the genus to be selected. Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

Consequently, there is no evidence that a sufficient number of representative species of this large genera were in the possession of the inventors at the time of filing. To satisfy the written description aspect of 35 U.S.C. 112, first paragraph, for a claimed genus of molecules, it must be clear that: (1) the identifying characteristics of the claimed molecules have been disclosed, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these; and (2) a representative number of species within the genus must be

disclosed. Because only three species of the claimed genus are disclosed, the claims fail to satisfy the written description requirement.

Claims 21, 30, 31, 35, 36, 39, 40 and 48-55 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the homo-dimerization affinity domains disclosed in the specification (SKPC, CKPS and AKPC), does not reasonably provide enablement for any homo- or hetero-multimerization affinity domain that has any size and structure, i.e., any amino acid sequence. As a result, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered in determining whether or not undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir.1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the breadth of the claims, (2) the nature of the invention, (3) the state of the prior art, (4) the relative skill of those in the art, (5) the predictability or unpredictability of the art, (6) the amount or direction or guidance presented, (7) the presence or absence of working examples, and (8) the quantity of experimentation necessary. Although the quantity of experimentation alone is

not dispositive in a determination of whether the required experimentation is undue, this factor does play a central role. For example, a very limited quantity of experimentation may be undue in a fledgling art that is unpredictable where no guidance or working examples are provided in the specification and prior art, whereas the same amount of experimentation may not be undue when viewed in light of some guidance or a working example or the experimentation required is in a predictable established art. Conversely, a large quantity of experimentation would require a correspondingly greater quantum of guidance, predictability and skill in the art to overcome classification as undue experimentation. In Wands, the determination that undue experimentation was not required to make the claimed invention was based primarily on the nature of the art, and the probability that the required experimentation would result in successfully obtaining the claimed invention. (Wands, 8 USPQ2d 1406). Thus, a combination of factors which, when viewed together, would provide an artisan of ordinary skill in the art with an expectation of successfully obtaining the claimed invention with additional experimentation would preclude the classification of that experimentation as undue. A combination of Wands factors, which provide a very low likelihood of successfully obtaining the claimed invention with additional experimentation, however, would render the additional experimentation undue.

Factors pertinent to this discussion include the predictability of the art, guidance in the specification, the breadth of claims and the amount of experimentation that would be necessary to use the invention.

The specification does not support the broad scope of the claims which encompasses any homo- or hetero-multimerization affinity domain (which reads on a polypeptide having any length and structure), because the specification does **not** establish: (A) the structures that are necessary for this activity, so that two monomers will bind and align in the proper orientation (the simple presence of a C residue does exclude or inhibit the formation of disulfide bonds

between this C residue and a C residue anywhere else on a second molecule of the monomer); (B) the general ability of random polypeptide sequences containing C residues to form homo-dimers (the elected invention for the claimed dimer), particularly random sequences used as linkers between functional domains; (C) a rational and predictable scheme for identifying the claimed multimerization affinity domain with an expectation of obtaining the desired result; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices are likely to be successful.

Without sufficient guidance, beyond that provided, obtaining the claimed multimerization affinity domain is unpredictable, and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. Applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)).

In view of the foregoing, the claims fail to satisfy the enablement requirement.

Claim Rejections - 35 USC § 112, second paragraph

In view of Applicants' cancellation of claim 27, the rejection in the previous Office action is withdrawn.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 21, 30, 31, 35, 36, 39, 40 and 48-55 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 21 recites several extension peptides, and it is not clear which polypeptides disclosed in the specification correspond to which claimed extension peptides. Claim 21 recites that the extension peptide, without the peptide linker and without the affinity domain for homo-multimerization, is a polypeptide that is 45 amino acids in length having a C at amino acid position 4. But, claim 50 recites that this extension peptide is a flexible peptide linker. The terms "flexible peptide linker" and several terms in claim 21, "extension peptide," "peptide linker," "peptide optional linker" and a peptide linker that is optionally present are confusing, as no structure is recited for any of these, apart from the minimal requirements for the "extension peptide." Thus, it is not clear if all of these polypeptides are the same thing, or if each polypeptide is different, or if some of these are the same thing, and, if so, which ones? Clarification and precise identification are required as to which polypeptides are the same as the extension peptide, which polypeptides are different, and what the identical features and the differences are between the extension peptide and the linker peptide. Further, the claims are confusing because claim 52, which recites the flexible peptide linker, which is the extension peptide, recites a polypeptide that need be only 10 amino acids long (the elected species is 20 amino acids long), and this polypeptide has no C's. Therefore, it cannot be the extension peptide/flexible peptide linker. This polypeptide may be the optional peptide linker of claim 21, as it has between 1 and 50 amino acids, but the identity of this polypeptide is not clear. Clear, unambiguous and definite claim language is required, as well appropriate correction of the claims.

Also, the limitation "wherein the one or more uncoupled cysteine residues are located at any position in the range of the first to forty-fifth amino acid residue from said binding domain directly bonded to either the first or the last amino acid residue of the extension peptide" implies that the Cys can be upstream of the first amino acid of the extension peptide. The term "directly

bonded" can be interpreted as a peptide bond between the Cys residue and the first amino acid residue of the extension peptide, particularly as the region between the binding domain and the functional domain may have multiple Cys residues. The location of the Cys residues is confusing. Are they in the extension peptide, in the peptide linker, in the multimerization domain, or in the peptide optional linker? It is unclear which of these pieces have Cys residues, how many Cys residues are in each and how the Cys residues are positioned relative to each other. Clear structures for the four polypeptides located between the binding domain and the functional domain must be recited. Clarification and appropriate correction are required.

In addition, the term "optionally further comprising a peptide linker consisting of 1-50 amino acid residues inserted between the functional group domain and the uncoupled cysteine residue which is closest to the functional group domain" is indefinite because one cannot determine what constitutes the extension peptide and what constitutes the linker peptide. For example, if one assumes that the closest Cys to the functional domain is at position 40 of the "extension peptide" and that the extension peptide is 45 amino acids long, if the peptide linker consists of 1-50 amino acids between the closet Cys to the functional domain and the functional domain, the peptide linker and the extension peptide would have to overlap based on how the claim defines the position of the Cys residue with respect to the peptide linker and the functional domain. If they overlap, how can one distinguish what is extension peptide and what is peptide linker? If a Cys residue is present in the overlapping region, how can one determine if the Cys is in the extension peptide or the peptide linker? The claim is indefinite, because, depending on where the extension peptide and the peptide linker are, boundaries that are undefined, the same Cys residue may or may not meet the limitation. Also, if the claim previously recited that the Cys residues are in the extension peptide, how can they now be in the linker? The only time that the extension peptide and the peptide linker will not overlap is when the last amino acid of

the extension peptide (C-terminus of the extension peptide) is an uncoupled Cys. Clarification and appropriate correction are required.

Claim Rejections - 35 USC § 102

In view of Applicants' amendments to the claims, the rejection of claims 21, 27, 30, 31, 35, 36, 39 and 40 under 35 U.S.C. 102(b) as being anticipated by Choi et al. ("A divalent immunotoxin formed by the disulfide bond between hinge regions of Fab domain," Bull Korean Chem Soc 22(12):1361-1365, 2001), as evidenced by Ogata et al. ("Processing of Pseudomonas exotoxin by a cellular protease results in the generation of a 37,000-Da toxin fragment that is translocated to the cytosol," J Biol Chem 265(33):20678-20685, 1990) is withdrawn.

In view of Applicants' amendments to the claims, the rejection of claims 21, 27, 30, 35, 36 and 39 under 35 U.S.C. 102(b) as being anticipated by Behringwerke AG (EP 501215 A2) is withdrawn.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rosanne Kosson whose telephone number is (571)272-2923. The examiner can normally be reached on Monday-Friday, 8:30-6:00, alternate Mondays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Nashaat Nashed can be reached on 571-272-0934. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Rosanne Kosson
Examiner, Art Unit 1652

rk/2008-12-23

/Delia M. Ramirez/

Primary Examiner, Art Unit 1652